U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2017/2018

Raquel Jorge Domingues Palhau

Fatores associados a recorrência em doentes com 5 anos de sobrevida após resseção de metástases hepáticas de cancro colo-rectal/ Factors associated with recurrence in patients with 5-year survival after resection of colorectal cancer liver metastases

março, 2018

Raquel Jorge Domingues Palhau

Fatores associados a recorrência em doentes com 5 anos de sobrevida após resseção de metástases hepáticas de cancro colo-rectal/ Factors associated with recurrence in patients with 5-year survival after resection of colorectal cancer liver metastases

Mestrado Integrado em Medicina

Área: Cirurgia Geral

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Dr. Marinho de Almeida

E sob a Coorientação de:

Dr. Renato Bessa de Melo

Trabalho organizado de acordo com as normas da revista:

HBP

Março, 2018

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Raquel Jorge Domingues Palhau, abaixo assinado, nº mecanográfico 200802286, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2018

Assinatura conforme cartão de identificação:

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Raquel Jorge Domingues Palhau

NÚMERO DE ESTUDANTE	E-MAIL
200802286	raquel_palhau@hotmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Fatores associados a recorrência em doentes com 5 anos de sobrevida após resseção de metástases hepáticas de cancro colo-rectal/ Factors associated with recurrence in patients with 5-year survival after resection of colorectal cancer liver metastases

ORIENTADOR

Dr. Marinho de Almeida

COORIENTADOR (se aplicável)

Dr. Renato Bessa de Melo

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 20/03/2018

Assinatura conforme cartão de identificação: 

Agradecimentos

Esta dissertação de mestrado é o resultado de muito trabalho, persistência e pesquisa que me fizeram crescer como futura médica e como pessoa.

A escolha da área do projeto não foi difícil uma vez que sempre me senti atraída pela Cirurgia Geral, nomeadamente na área Hepatobilio-pancreática, provavelmente pela forma cativante como o meu orientador, Dr. Marinho de Almeida, me proporcionou viver o dia-a-dia do cirurgião e a quem eu agradeço todo o conhecimento transmitido e disponibilidade ao longo deste último ano.

Ao meu co-orientador Renato Bessa de Melo por todos os reparos e comentários que facilitaram o desenvolvimento e orientação do trabalho.

Ao meu amigo Joaquim Monteiro que se prontificou na colaboração da elaboração da estatística permitindo o fecho deste trabalho.

Ao serviço de Cirurgia Geral dirigido pelo Dr. Costa Maia e ao Centro de referência de Cancro Hepatobilio-pancreático em coordenação pelo Dr. Luís Graça que possibilitaram a realização do estudo.

E um especial obrigado ao meu pai, a quem posso agradecer me ter dado todas as oportunidades e apoio incondicional de frequentar este curso, à minha irmã e ao meu namorado, incansáveis no incentivo, apoio e carinho.

A todos os que caminharam comigo.

“Devagar se vai ao longe”.

,

Um sincero obrigada!!

Raquel Palhau

Factors associated with recurrence in patients with 5-year survival after resection of colorectal cancer liver metastases

Raquel Palhau[1], Marinho de Almeida[1,2] MD PhD e Renato Bessa de Melo[1,2] MD

[1]Faculty of Medicine of Porto University, Alameda Prof. Hermâni Monteiro, 4200-319 Porto, Portugal

[2]HBP Unit, Department of Surgery of São João Hospital Center, Alameda Prof. Hermâni Monteiro, 4200-319 Porto, Portugal

Correspondence: Email: raquel_palhau@hotmail.com

Address: Faculty of Medicine of Porto University, Alameda Prof. Hermâni Monteiro, 4200-319 Porto, Portugal

Conflict of interest Disclosures: None to report

ABSTRACT

Introduction: Colorectal cancer (CRC) is associated with liver metastases up to 35% of cases. Even after performance of liver surgery with curative intent and absence of extra-hepatic involvement, recurrence is frequent. Therefore, the identification of factors associated with recurrence and disease-free survival (DFS) could provide better selection of candidates for liver surgery.

Patients and methods: Patients submitted to liver surgery for colorectal liver metastases (CRLM), in São João Hospital Center (CHSJ), with 5-years survival and no extra-hepatic disease were studied. Data was collected and analysed to identify recurrence and DFS associated factors.

Results: Recurrence occurred in 20 patients (52.63%) and 27 patients (71.05%) are alive and in remission with a DFS mean of 73 months. Statistical significance was found for early relapse associated with left side colon cancer ($p < 0.05$) and late recurrence with positive margins ($p < 0.043$). Also, patients with less than 5 metastases had at least double DFS ($p < 0.033$).

Conclusion: DFS is optimized when less than 5 lesions are present. Faster relapses occur in right colon cancer, although DFS was similar independently of primary´s tumour site. It is important to increase size sample and compare to those without 5-year survival for further conclusions.

Keywords: colorectal cancer, hepatic metastases, hepatic resection, recurrence, disease free survival

INTRODUCTION

Colorectal cancer (CRC) remains the third cause of malignancy death worldwide [1,2]. There hasn´t been found any association in gender but it´s well recognise that men present higher mortality and incidence rates, although rate of CRC deaths appear similar between both genders [2,3]. Primary prevention is the first step towards several recognized risk factors, such as diet, physical activity, weight, smoking and alcohol [4]. Most developed countries divulged screening progress, especially for individuals at risk (Inflammatory Bowel Disease and personal or family history of CRC), promoting early detection, as well as better and improved treatments that have allowed an increase of Overall Survival (OS) [2,3,5].

When suspicion of CRC, full work up, including thoracic/abdominal/pelvic computed tomography (CT), should be performed and in doubt an MRI, in order to verify resectability of primary tumour, liver metastases and the existence of extra-hepatic disease [4]. The use of enhance imaging techniques allows the identification of colorectal liver metastases in 35% of cases [6–8]. Furthermore, synchronous metastases are in a majority of cases, 70-80%, confined to the liver [9]. And eventually, more than half of CRC patients will develop liver metastases [9,10]. Until now, hepatic surgery as proven to be the most effective treatment increasing OS [4,11–14] with mortality rates after hepatic surgery described as lower than 5% [14–16] and 5-years survival between 16-74% according to Kansas et al review and meta-analysis [12].

Nowadays, new therapies such as transarterial chemoembolization (TACE); systemic chemotherapy, with or without biologic agents; radioembolization with Yttrium-90 (useful to refractory disease) and radiofrequency ablation (RFA) have been used in association with surgery or even as a substitute for those inapt for surgery [4,17,18]. All local therapies with no exception have been proven to be inferior to surgery when used alone [4,5,19]. However, if the use of some of these therapies need more studies to support more consistent applications, the use of chemotherapy has been widely established [4]. Even though, perioperative chemotherapy in resectable liver metastases is still somewhat debatable and should be applied individually to patient characteristics [5,20], it achieves great importance in converting irresectable liver metastases in resectable ones, especially because the majority of patients appear to have irresectable lesions [4,5,17,21,22]. It has been described that patients with successful conversion of irresectable liver metastases can even achieve 33 to 76% survival at 5-years [23–25].

Given the evolve of all medical areas (pathology, oncology, radiology and surgery) and the different therapeutic options available is extremely important that this patients should be referred to centers with multidisciplinary teams that are better prepared to provide better decisions for individual patients regarding management and treatment, decreasing delays, costs and increasing OS [5,19,26].

If, on one hand, 5-years survival has been increasing due to a better medical treatment-management, on the other hand recurrence is still frequent and affects around 70% within less than 2-years [27]. And so, a close up follow up is needed for patients treated for colorectal liver metastases (CRLM). This is usually done by measuring carcinoembryonic antigen (CEA) levels and performance of CT scan on regular basis, since they´re the most cost-effective for detecting recurrence [28]. Still, a close-up surveillance is necessary and it is also imperative that we understand which factors could contribute to a intra or extra-hepatic recurrence, in order to improve patient treatment and patient selection.

The aim of the present study is to study factors that could correlate to recurrence and DFS, in patients that are alive 5-years after CRLM resection.

PATIENTS AND METHODS

All patients submitted to resection of CRLM in the Department of Hepatobiliary Surgery of São João Hospital Center (CHSJ), from 2006 to 2012, were identified in the Department´s database.

One by one, each patient was analysed, being selected only those with the following characteristics:

- 5-year follow-up in CHSJ
- No extra-hepatic disease
- Hepatic resection with curative intent

Data for these patients were afterwards extracted from the Hospital´s database, which included clinical records from medical consultations (oncology, colon surgery, hepatic surgery), imaging exams (CT), full blood workup, anatomopathological results and surgical registries. No patients or family patients were contacted during the fulfil of this study. And all measures were taken protecting the anonymity of these patients. This study was approved by the Ethical Comity (CES) of CHSJ, number 270/17.

Patient selection is represented in Figure 1.

The following data was searched: age, gender, site and histopathology from the primary tumour, time of hepatic metastases and characteristics (size, number and localization), preoperative CEA levels, hepatic surgical resection, complications, time of recurrence and time of disease free.

Patients with the primary tumour located less than 15 cm from the anal margin were defined as rectum, as designed in the nomenclature of the Portuguese Society of Surgery. Right side colon cancer (RCC) was considered between cecum and proximal transverse and left side colon cancer (LCC) included distal transverse, descending colon

and sigmoid.

Complete lymphadenectomy was considered when at less 12 lymph nodes were removed.

DFS was considered the time interval between first liver resection and secondary recurrence of CRC (colon, liver, lung or other extra-hepatic sites). Early relapse was defined as within less than 12 months after CRLM resection.

Data were pooled and analysed using SPSS v. 25 software. Numerical variables were described using mean or median with their dispersion measures (standard deviation and 95% confidence interval or 5 and 95 percentiles). Categorical variables were described in relative frequencies. In the comparison between groups, independent t-student, ANOVA or Pearson´s Chi-Square tests were used, according to the type of comparison, with $\alpha = 0.05$.

RESULTS

Patient Demographics

From the 38 patients that fitted the inclusion criteria's 15 were women and 23 were men. The median age (at time of hepatic resection) was 64.32 as described in Table 1 (range 40 to 85), 14 were age 70 or older.

Primary Lesion

As presented in Table 1, 28 patients had their primary lesions in the colon. The majority, 52.6 %, had LCC, followed by rectal disease (26.3%) and RCC, (21.1%). Patients with RCC presented mean age of 73.38, versus 62.95 in LCC and 59.8 in rectum. In 20 patients, 47.5%, the primary tumour was associated with regional lymph node metastases (3 in RCC, 11 in LCC and 6 in rectum). The primary tumour was associated with synchronous hepatic metastases in half of the patients (2 RCC, 10 in LCC and 7 in rectum) and in 23.7% of the patients within less than a year. Duo to occlusion (4) or perforation (2), six patients were submitted to urgent colon resection surgery.

Adjuvant chemotherapy, after the primary tumour resection, was given to all patients but seven, one due to comorbidities and in other three because of the delayed of oncological consultation after primary tumour resection. No explanation was found in the other three.

Histopathology

In seven patients' histology of the primary tumour was not accounted for, since surgery was performed in the exterior, and therefore could not be access through the Hospital´s database. In this cohort, 75% of patients presented primary tumours that penetrated through the *muscularis propria* (T3). A majority of patients, 52.6%, presented positive lymph nodes (N1 or N2), however it should be accounted that 25.7% of the patients had less than 12 lymph nodes removed, which could underestimate this percentage. Results are presented in Table 1. Interestingly enough, in all 6 patients subject to urgent colon resection complete lymphadenectomy was performed. Invasion of the visceral peritoneum was present in 5 patients, 4 in LCC and 1 RCC.

In 13 patients KRAS mutation was searched, five of them turn out positive, but in only two biologic agents were used.

Neoadjuvant systemic and local therapy

There were not used local therapies in these patients. Sixteen patients received neoadjuvant chemotherapy (42.11%), twelve presented synchronous hepatic metastases and in the other four cases chemotherapy was used to turn the hepatic lesions resectable. The neoadjuvant chemotherapy scheme more often used was FOLFOX or FOLFIRI (10

of 16) often associated in biologic agents, when more than four hepatic lesions or bilobular disease was present. Only in three people capecitabine was administer and, in one patient, irinotecan was associated.

Liver Tumour

The median number of liver metastases was 3 (range 1 to 15). Single liver tumour was present in seventeen patients (almost 45%). Generally speaking 78.9% present less than 5 liver metastases, 10.5% between 5 and 10 and 10.5% over 10 hepatic metastases. The mean size of the biggest metastases was 3 cm (range 0.6 and 6) and only 4 patients presented tumours larger than 5 cm.

CEA levels

Preoperative CEA levels was not available in nine patients. Overall, 63.3% present levels under 10 ng/dL, and 20% levels over 30 ng/dL. The mean CEA levels was 95.93 ng/dL, although it should be stated that tree patients presented values of 442.2, 739 and 1411.8 ng/dL, which can misrepresent this cohort.

Surgical Resections

First and second liver resections performed are described in Table 2. Complete or extended lobectomy were complemented with liver metastasectomy in 28.9% of cases. On average two and half hepatic segments were resected, range 1 to 6. Ten patients were submitted to new hepatic resection, in this group, one patient underwent radioablation in association to liver resection. No other complementary technics were used.

Simultaneous resection of the primary tumour was performed in five patients, 13.16%, and two patients underwent liver resection prior primary tumour resection (reverse approach). In seventeen patients clamping of the hepatic pedicle was performed. After initial hepatic resection, new hepatic resection was performed in 10 patients (26.32%). Two stage hepatectomy was executed in three patients, these patients presented multiple metastases with bilobular disease.

Only one patient was treated with other local technics combined with hepatic surgery (radioablation), after intra-hepatic recurrence.

Perioperative Results

Mean hospital stay was 11 days (range 5 to 47). Five patients required perioperative blood transfusion. Of the 38 patients, four of them had post-operative complications, 10.56%. Two developed intra-abdominal abscess collections, one of them resolved with percutaneous drainage, whereas for the other one new surgical approach was needed and a drain was left in place. Other one developed atrial fibrillation being successfully treated with amiodaron.

As for the last developed sepsis and exploratory laparotomy was required and although the source was not to be discovered during the procedure the patient had a following good recovery.

Adjuvant therapies

Only 3 patients, 7.89%, did not receive adjuvant chemotherapy. Two presented a single hepatic lesion and the other three lesions but less than 0.6cm. In ten patients FOLFOX was used isolated, and in three patients' bevacizumab or cetuximab was co-administered, six patients used FOLFIRI, one of them simultaneously with bevacizumab, one used irinotecan plus cetuximab, another one panitumumab, four XELOX and eight capecitabin alone.

Follow-up

After discharge, patients were reviewed after, first postoperative month and every 3 months in the first year, with evaluation of tumour markers (CEA), liver function tests, abdominal and chest CT scans performed after 6 and 12 months. After 3 years of follow up with no recurrences, annual follow-up was considered, as well as discharged to family doctor after 5/6 years. Discontinuation of the treatment was decided in the absence of any persistent or recurrent tumour.

Time recurrence

Of the 38 patients, 18 patients (47.37%) did not relapse and 20 patients relapsed within 19.45 months after hepatic surgery (range 3 to 39). Overall there was no statistical difference in age, gender, histopathology from the primary tumour, time of hepatic metastases and characteristics (size, number and localization), preoperative CEA levels or bilobular hepatic disease. However, two variables presented statistical significance ($p < 0.05$) as is presented in Table 1. In this sample, early relapse was present only in those with LCC ($p < 0.05$). All R1 patients presented late relapse. However, late relapse was more frequent in patients with negative surgical margins (78.6% versus 21.4%, $p < 0.043$).

No relapse was found after 39 months.

Disease free Survival

Hepatic lesions were the only variables that appear to have statistical significance ($p < 0.05$), as observed in Table 3. Patients with less than 5 hepatic metastases had at least double time DFS (median of 86 months versus 41.5 and 22). Although, timing of hepatic metastases, hepatic size metastases and surgical margins do not present statistical significance in this cohort, this should be confirmed with a greater size sample. Early metachronous hepatic metastases appear to have higher DFS then synchronous and late metachronous, median 105. 81 and 77, respectively ($p < 0.061$).

The presence of hepatic metastases with less than 5 cm looks to enhance DFS when compared to those larger than 5 cm (median 82 months versus 43.5 months, $p < 0.61$). Finally, patients with negative surgical margins present a median DFS of 82.5 months, whereas patients with positive margins present only 18 months ($p < 0.66$).

Twenty-seven patients are presently in remission (71.05%).

DISCUSSION

Given the nature of the present study, several problems should be pointed out. This is a retrospective study which conditioned the collection of data, namely, some of the variables studied were non-existent or even incoherent, and therefore could not be used. Also, in the absent of a control group, patients that have died before the 5-year follow up, the factors in lighted in this study cannot be determined as prognostic factors and considered only associated factors, given that certain characteristics could be inherent to the present population with CRC stage IV.

In this study, it is estimated an 31.7% survival rate of at 5-year follow up, 38 patients of 120. Nevertheless, it should be stated that 3 patients were excluded due to extra-hepatic disease at diagnoses, therefore a 34.2% survival would be more accurate. There was no significant difference between gender or age regarding relapse as some studies agree [13,29]. Still, elderly appear to present worse outcome [30].

Statistical significance was found in primary tumour localization. Patients with LCC were the only ones associated with early relapse ($p = 0.05$). Is it then correct to assume, that patients with early relapse with RCC or rectal cancer present a survival of less than 5 years? Many studies report worse prognosis and survival for those with RCC when compare to LCC, not only due histopathologic characteristic but to late clinical presentation and different metastatic sites [31–33]. Also RCC seems associated more frequently to female gender and older patients [31–33]. And it comes to no surprise that rectum cancer presents worse outcomes, earlier recurrence and worse OS even in the absence of hepatic metastases [34].

Although, in general, histopathology differences are presented as a factor to worst prognosis, in this study was difficult to evaluate the impact of KRAS mutation since less than half of the patients had KRAS mutation searched. Presently it is stablished that RAS testing should be carried out in all patients with CRLM [5]. KRAS mutation usually presents higher rates in RCC [32], and it´s been described that their presence can even decrease survival in 20% [35].

Positive lymph nodes did no correlate to recurrence, as some stat in the literature [36,37]. Regardless, others considered their presence no only an important prognostic factor for recurrence but also for OS, [13,29], thus being included as variables for predicting scores for recurrence or survival. Positive lymph nodes are more specifically associated with early recurrence [38].

Timing of hepatic metastases was defined according to a multidisciplinary international consensus. [20]. In this cohort synchronous CRLM was present in half of the patients, and although it is known to present poor prognostic, it did not appear to relate to early recurrence. Moreover, according to several specialists consensus synchronous CRLM are associated with worse prognosis, especially when compared to late metachronous [5,20]. Curious enough in the

present study, not only early metachronous presented a higher DFS, synchronous metastases surpassed late metachronous, without reaching statistical significance, which comes to an agreement in some studies that timing of hepatic metastases do not affect OS or DFS [14]. However, comparison to those deceased before 5year follow up would be require to encounter a more reliable conclusion.

Number and size of hepatic metastases has been considered an important factor in predicting recurrence and OS, even though the exact size and number are still debateable. In the present study no statistical significance was found in CRLM characteristics regarding recurrence, as also described in some studies [27,39] or regarding solely size [38]. However most studies included over 1 or 3 hepatic metastases as a predicting factor for recurrence [13,30,38]. But a higher DFS was seen when less than 5 hepatic lesions were present, conduction to at least double time disease free (median of 86 months versus 41.5 and 22 ($p < 0.033$).

As for CEA levels two things should be pointed out in the present study, in 8 patients CEA levels perioperative were not available, thus diminishing sample size, and in 16 of them neoadjuvant QT was used prior surgery that influence their value. So even if in a hand full of cases increased CEA levels indicted a recurrence, as found in literature [28], this factor was not statistically associated with recurrence or DFS.

The surgical approach although described was not statistically studied. It is described in the literature that simultaneous resection in synchronous CRLM is safe and associated with decrease time in hospital admission, however this should not be applied in those intended to major hepatectomy and resection of over 3 segments duo to higher risk of complications, [40,41]. Other studies suggest that the classical approach was in general associated with better OS and DFS [42]. Also, in this study patients who were submitted to two stage hepatectomy presented bilobular disease and multiple metastases, and it has been showed that even in the presence of extensive metastatic disease, those who complete two stage hepatectomy can achieve comparable OS as those submitted to Classical approach and one stage hepatectomy regardless of recurrence [43].

A secondary procedure was performed in 10 patients and no more than 3 segments were removed. This is consistent with former studies that acknowledge major hepatectomy as being less frequent in a second hepatectomy [44,45]. Moreover, a secondary hepatectomy may well be associated with better OS [45].

As described, only one patient was subjected to other local technics, specifically radioablation, combined with liver surgery. NCCN guidelines suggests the use of radioablation only in those with recurrent small hepatic metastases with adequate margins, [4], adding the existence of limited data. Interestingly enough, studies have shown that radioablation is associated with increase hepatic recurrence when compared to surgery alone [27,46].

In the present study statistical significance was obtained in surgical margins. Positive margins were associated with early recurrence, although negative margins presented a majority in this group. Most studies support that R0 margins are not only associated with less recurrence but also to an increase in OS [27,30,38,47]. However, some like Hass et al, don´t agree that R1 margins have impact on OS [48]. Even thought, surgical margins did not reach a statistical significance in DFS, $p < 0.066$, a propensity score matching analysis concluded that R1 margins are still an impacting factor in OS and DFS, even when recurrence has been balanced [49].

As a final remark, twenty patients of the present study presented relapse within 19.45 months after hepatic surgery (range 3 to 39). Twenty-seven patients are presently in remission (71.05%). Even though we analysed those with 5-year follow up we have patients that actually present till 10 years (120 months) survival after hepatic resection. So in some we can agree with studies that stat that patients that do not present any recurrence before 5-years that they are "cured" [50], seen no patients in this study present relapse after 60 months. However, this should be pursued in patients with less than 5-years survival.

CONCLUSION

Summarizing, more than half of patients, with 5-year survival, and LCC have faster relapse. Although DFS was similar independently of the site of the primary tumour. Also, DFS is best for patients with less than 5 lesions. In a greater size sample timing, number, size of hepatic metastases and surgical margins should be study as possible factors that could enhance DFS, even though in this cohort statistical significance was not reached.

The existence of several discrepancies in the nomenclature regarding the factors associated with recurrence and OS calls for the performance of studies at greater scale, namely in different specialized centers. Is it not wise to question that, since studies are being performed in different populations, the same factor could be more determinant in some populations and have less impact in others. Additionally, the same factors could be misevaluated taking into account distinct cut-offs. There is no surprise that, consensus prevenient from specialist panels pronounces that treatment and surgical approach should always be taken into consideration by multidisciplinary teams that considered the inherent clinical characteristic of the patient itself.

This study should be criticized duo to small size sample and the lack of comparation with patients' deceased before 5-year follow up. However, this could be the start of a large-scale study that could not only turn to a development of a solid score but also have greater implication as to the choosing of more adequate patients for surgery and the choosing of those in which a more aggressive therapy should be performed, for starts in CHSJ.

REFERENCES

1. Haggar, F. a, Boushey, R. P. & Ph, D. Colorectal Cancer Epidemiology : Incidence , Mortality , Survival , and Risk Factors. *Clin. Colon Rectal Surg.* **6,** 191–197 (2009).
2. Siegel, R. L. *et al.* Colorectal Cancer Statistics , 2017. **67,** 177–193 (2017).
3. Pinto, C. G., Paquete, A. T. & Pissarra, I. Colorectal cancer in Portugal. *Eur. J. Heal. Econ.* **10,** (2010).
4. Cancer, C. Colon Cancer. *Natl. Comprehensice Cancer Netw.* **2.2017,** (2017).
5. Van Cutsem, E. *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann. Oncol.* **27,** 1386–1422 (2016).
6. Weledji, E. P. Centralization of liver cancer surgery and impact on multidisciplinary teams working on stage IV colorectal cancer. *Oncol. Rev.* **11,** 74–80 (2017).
7. ZACHARAKIS, M. *et al.* Predictors of Survival in Stage IV Metastatic Colorectal Cancer. *Anticancer Res* **30,** 653–660 (2010).
8. Valderrama-Trevino, A. I., Barrera-Mera, B., Ceballos-Villalva, J. C. & Montalvo-Jave, E. E. Hepatic Metastasis from Colorectal Cancer. *Euroasian J. Hepato-Gastroenterology* **7,** 166–175 (2017).
9. Manfredi, S. *et al.* Epidemiology and management of liver metastases from colorectal cancer. *Ann. Surg.* **244,** 254–259 (2006).
10. Zarour, L. R. *et al.* Colorectal Cancer Liver Metastasis: Evolving Paradigms and Future Directions. *Cmgh* **3,** 163–173 (2017).
11. Imamura, H. *et al.* Single and multiple resections of multiple hepatic metastases of colorectal origin. *Surgery* **135,** 508–517 (2004).
12. Kanas, G. P. *et al.* Survival after liver resection in metastatic colorectal cancer: Review and meta-analysis of prognostic factors. *Clin. Epidemiol.* **4,** 283–301 (2012).
13. Fong, Y., Fortner, J., Sun, R. L., Brennan, M. F. & Blumgart, L. H. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surr* **230,** 309-18-21 (1999).
14. Malik, H. Z. *et al.* Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. *Ann. Surg.* **246,** 806–814 (2007).
15. Cummings, L. C., Payes, J. D. & Cooper, G. S. Survival after hepatic resection in metastatic colorectal cancer: A population-based study. *Cancer* **109,** 718–726 (2007).
16. Oba, M. *et al.* Discrepancy Between Recurrence-Free Survival and Overall Survival in Patients with Resectable Colorectal Liver Metastases: A Potential Surrogate Endpoint for Time to Surgical Failure. *Ann. Surg. Oncol.* **21,** 1817–1824 (2014).
17. Maher, B., Ryan, E., Little, M., Boardman, P. & Stedman, B. The management of colorectal liver metastases. *Clin. Radiol.* **72,** 617–625 (2017).
18. Kopetz, S. *et al.* Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J. Clin. Oncol.* **27,** 3677–3683 (2009).
19. Fiorentini, G. *et al.* Multidisciplinary approach of colorectal cancer liver metastases. *World J. Clin. Oncol.* **8,** 190 (2017).

20. Adam, R. *et al.* Managing synchronous liver metastases from colorectal cancer: A multidisciplinary international consensus. *Cancer Treat. Rev.* **41,** 729–741 (2015).
21. Adam, R., Hoti, E. & Bredt, L. C. Oncosurgical strategies for metastatic liver cancer. *Cirugía española* **89,** 10–9 (2011).
22. Gruber-Rouh, T. *et al.* Current strategies in interventional oncology of colorectal liver metastases. *Br. J. Radiol.* **89,** (2016).
23. Adam, R. *et al.* Rescue Surgery for Unresectable Colorectal Liver Metastases Downstaged by Chemotherapy. *Trans. ... Meet. Am. Surg. Assoc.* **CXXII,** 242–256 (2004).
24. Maeda, Y., Shinohara, T., Nagatsu, A., Futakawa, N. & Hamada, T. Long-Term Outcomes of Conversion Hepatectomy for Initially Unresectable Colorectal Liver Metastases. *Ann. Surg. Oncol.* 242–248 (2015). doi:10.1245/s10434-015-4460-0
25. Folprecht, G. *et al.* Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann. Oncol.* **25,** 1018–1025 (2014).
26. Prades, J., Remue, E., van Hoof, E. & Borras, J. M. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health Policy (New. York).* **119,** 464–474 (2015).
27. De Jong, M. C. *et al.* Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: An international multi-institutional analysis of 1669 patients. *Ann. Surg.* **250,** 440–447 (2009).
28. Primrose, J. N. *et al.* Effect of 3 to 5 Years of Scheduled CEA and CT Follow-up to Detect Recurrence of Colorectal Cancer. *Jama* **311,** 263 (2014).
29. Rees, M., Tekkis, P. P., Welsh, F. K. S., O'Rourke, T. & John, T. G. Evaluation of Long-term Survival After Hepatic Resection for Metastatic Colorectal Cancer. *Ann. Surg.* **247,** 125–135 (2008).
30. Imai, K. *et al.* Early Recurrence After Hepatectomy for Colorectal Liver Metastases: What Optimal Definition and What Predictive Factors? *Oncologist* **21,** 887–894 (2016).
31. Meguid, R. a, Slidell, M. B., Wolfgang, C. L., Chang, D. C. & Ahuja, N. Is There a Difference in Survival Between Right-Versus Left-Sided Colon Cancers? *Ann. Surg.* **15,** 2388–2394 (2011).
32. Nitsche, U. *et al.* Right sided colon cancer as a distinct histopathological subtype with reduced prognosis. *Dig. Surg.* **33,** 157–163 (2016).
33. Benedix, F. *et al.* Comparison of 17,641 patients with right- and left-sided colon cancer: Differences in epidemiology, perioperative course, histology, and survival. *Dis. Colon Rectum* **53,** 57–64 (2010).
34. van der Sijp, M. P. L. *et al.* Differences between colon and rectal cancer in complications, short-term survival and recurrences. *Int. J. Colorectal Dis.* **31,** 1683–1691 (2016).
35. Knowles, B., Welsh, F. K. S., Chandrakumaran, K., John, T. G. & Rees, M. Detailed liver-specific imaging prior to pre-operative chemotherapy for colorectal liver metastases reduces intra-hepatic recurrence and the need for a repeat hepatectomy. *Hpb* **14,** 298–309 (2012).
36. Nagashima, I., Takada, T., Nagawa, H., Muto, T. & Okinaga, K. Proposal of a new and simple staging system of colorectal liver metastasis. *World J. Gastroenterol.* **12,** 6961–5 (2006).
37. Adam, R. *et al.* Concomitant extrahepatic disease in patients with colorectal liver metastases: When is there a

place for surgery? *Ann. Surg.* **253,** 349–359 (2011).

38. Viganò, L. *et al.* Early Recurrence After Liver Resection for Colorectal Metastases: Risk Factors, Prognosis, and Treatment. A LiverMetSurvey-Based Study of 6,025 Patients. *Ann. Surg. Oncol.* **21,** 1276–1286 (2014).
39. Hayashi, M. *et al.* Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. *BMC Surg.* **10,** 27 (2010).
40. Mekenkamp, L. J. M. *et al.* Clinicopathological features and outcome in advanced colorectal cancer patients with synchronous vs metachronous metastases. *Br. J. Cancer* **103,** 159–164 (2010).
41. Reddy, S. K. *et al.* Simultaneous resections of colorectal cancer and synchronous liver metastases: A multi-institutional analysis. *Ann. Surg. Oncol.* **14,** 3481–3491 (2007).
42. She, W. H. *et al.* Defining an optimal surgical strategy for synchronous colorectal liver metastases: Staged versus simultaneous resection? *ANZ J. Surg.* **85,** 829–833 (2015).
43. Tsai, S. *et al.* Two-stage strategy for patients with extensive bilateral colorectal liver metastases. *Hpb* **12,** 262–269 (2010).
44. Luo, L. X., Yu, Z. Y., Huang, J. W. & Wu, H. Selecting patients for a second hepatectomy for colorectal metastases: An systemic review and meta-analysis. *Eur. J. Surg. Oncol.* **40,** 1036–1048 (2014).
45. Neal, C. P. *et al.* Repeat hepatectomy is independently associated with favorable long-term outcome in patients with colorectal liver metastases. *Cancer Med.* **6,** 331–338 (2017).
46. Tanis, E. *et al.* Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. *Eur. J. Cancer* **50,** 912–919 (2014).
47. Sadot, E. *et al.* Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann. Surg.* **262,** 476-85–5 (2015).
48. De Haas, R. J. *et al.* R1 resection by necessity for colorectal liver metastases: Is it still a contraindication to surgery? *Ann. Surg.* **248,** 626–636 (2008).
49. Memeo, R. *et al.* Margin Status is Still an Important Prognostic Factor in Hepatectomies for Colorectal Liver Metastases: A Propensity Score Matching Analysis. *World J. Surg.* (2017). doi:10.1007/s00268-017-4229-7
50. Imai, K. *et al.* Potential of a cure in patients with colorectal liver metastases and concomitant extrahepatic disease. *J. Surg. Oncol.* **115,** 488–496 (2017).

TABLES AND ILLUSTRATIONS

Figure 1: Diagram representing patient selection from the Department´s Database.

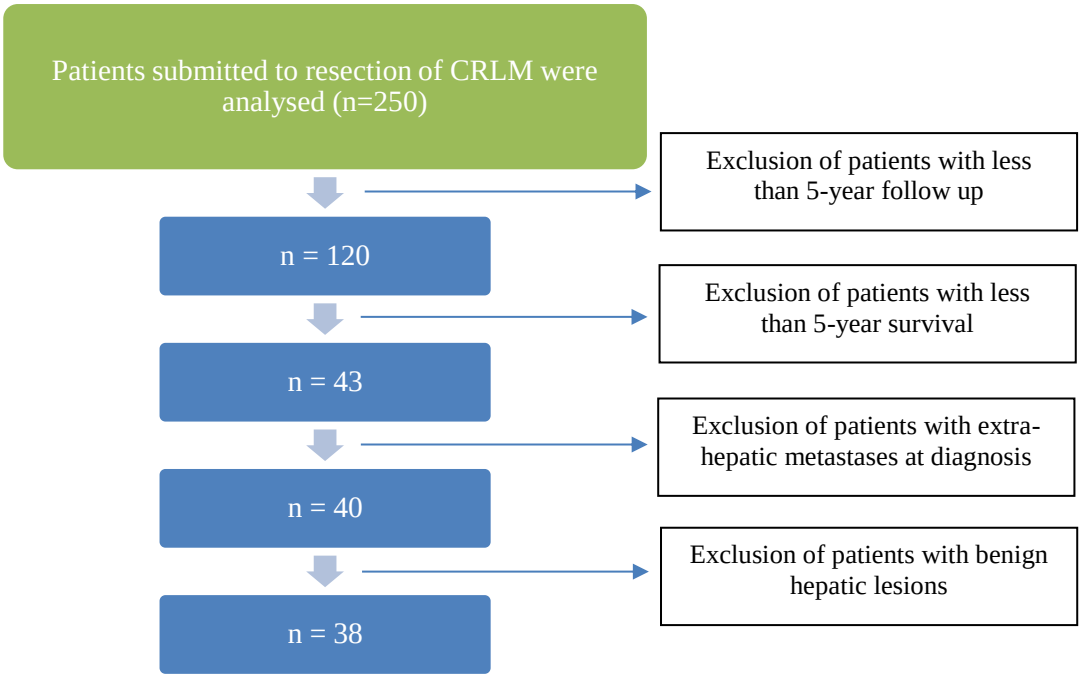

TABLE 1: FACTORS ASSOCIATED WITH RECURRENCE

	Total sample (n=38)	*No-relapsed (n=18)*	*Early Recurrence (n=15)*	*Late Recurrence (n=5)*	*P (α= 0.05)*
Age (years)	64.32±11.00 (60.70 – 67.93)	68.11±9.36 (63.46 – 72.76)	61.07 ±12.58 (54.10 – 68.03)	60.40±8.39 (49.99 – 70.81)	0.129
Gender (%)					
Male	60.5	61.1	53.3	80	0.571
Female	39.5	38.9	46.7	20	
Primary tumour localization					
RCC	21.1	27.8	20.0	0	
LCC	52.6	44.4	46.7	**100***	***<0.05**
Rectum	26.3	27.8	33.3	0	
T (%), n=36					
2	11.1	11.8	14.3	0	
3	75	70.6	78.6	80	0.820
4	13.9	17.6	7.1	20	
N (%)					
0	47.4	55.6	40	40	
1	36.8	27.8	46.7	40	0.842
2	15.8	16.7	13.3	20	
Lymphadenectomy (n=35)					
Non complete	25.7	27.8	25	20	0.938
Complete	74.3	72.2	75	80	
Visceral peritoneum invasion (n=31)					
No	83.9	82.4	90	75	0.764
Yes	16.1	17.6	10	25	
Timing hepatic metastases (%)					
Synchronous	50	44.4	53.3	60	
Metachronous					0.610
Early	23.7	33.3	20	0	
Late	26.3	22.2	26.7	40	
Hepatic lesions number (%)					
<5	78.9	88.9	73.3	60	
5-10	10.5	5.6	13.3	20	0.656
>10	10.5	5.6	13.3	20	
Hepatic size metastases (%, n=37)					0.728
<5	89.2	88.9	92.9	80	
5-10	10.8	11.1	7.1	20	
Pre-op CEA levels (n=30)					
<10	63.3	56.3	77.8	60	0.615
10-30	16.7	25	0	20	
>30	20.0	18.8	22.2	20	
Bilobolar hepatic metástases (%, n=37)					
Absent	64.9	72.2	57.1	60	0.655
Present	35.1	27.8	42.9	40	

ASA (%)					
I	65.8	61.1	73.3	60	0.900
II	13.2	16.7	6.7	20	
III	21.1	22.2	20	20	
Surgical margins (n=37)					
Negative	91.9	100	**78.6***	100	***0.043**
Positive	8.1	0	**21.4***	0	

TABLE 2: SURGICAL PROCEDURES

	Primary Liver procedure (n)	Secondary Liver procedure (n)
Metastasectomy	11	1
Segmentectomy	7	3
Bisegmentectomy	6	4
Trisegmentectomies	5	2
Four segments resected	3	0
Five segments resected	6	0

TABLE 3: FACTORS ASSOCIATED WITH DISEASE FREE SURVIVAL

		Disease free survival (n=38, months) Median(P5-P95)	*P*
Total		82 (9.65 – 127.10)	
Sex			
	Male	82.00 (4.4-128)	0.834
	Female	82.00 (11 – 127)	
Primary tumour localization			
	RCC	77 (19 – 110)	
	LCC	85.5 (3.35-128.9)	0.798
	Rectum	81.5 (15-112.2)	
T, (n=36)			
	2	80.5 (6,1-103.5)	0.611
	3	86 (6.2-128.2)	
	4	72 (10-102)	
N			
	0	82 (3-127)	0.897
	1	80 (15-122.5)	
	2	88,5 (10-117)	
Lymphadenectomy (n=35)			
	Incomplete	81.5 (5.45-125.15)	0.213
	Complete	89 (15-125.5)	
Visceral peritoneum invasion (n=31)			
	No	84 (12.4-128.3)	0.295
	Yes	72 (10-102)	
Timing hepatic metastases (%)			
	Synchronous	81 (12.75-127.9)	
	Metachronous		0.061
	Early	105 (22-121)	
	Late	77 (11-125.1)	
Hepatic lesions number (%)			
	<5	86 (12.75-127.9)	***0.033**
	5-10	22 (11-85.5)	
	>10	41.5 (3-70.75)	
Hepatic size metastases (%, n=37)			
	<5	82 (10.70-127.60)	0.061
	5-10	43.5 (3-96.75)	
Pre-op CEA levels (n=30)			
	<10	88 (10-124)	0.412
	10-30	82 (74-111.5)	
	>30	77 (3-86.75)	
Bilobolar hepatic metástases (%, n=37)			
	Absent	84 (11.25-127.75)	0.408
	Present	81 (3-127)	
ASA (%)			
	I	83 (10.3-128.4)	
	II	80 (17-110)	0.507
	III	77.5 (3-87.5)	
Surgical margins (n=37)			
	Negative	82.5 (8.25-127.5)	0.066
	Positive	18 (17-18)	

ATTACHMENTS

Author guidelines for HBP magazine

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 1365-182X

DESCRIPTION

To visit the *HPB* journal website click here: http://www.hpbonline.org/

HPB is an international forum for clinical, scientific and educational communication.

Twelve issues a year bring the reader leading articles, expert reviews, original articles, images, editorials, and reader correspondence encompassing all aspects of benign and malignant hepatobiliary disease and its management. *HPB* features relevant aspects of clinical and translational research and practice.

Specific areas of interest include HPB diseases encountered globally by clinical practitioners in this specialist field of gastrointestinal surgery. The journal addresses the challenges faced in the management of cancer involving the liver, biliary system and pancreas. While surgical oncology represents a large part of *HPB* practice, submission of manuscripts relating to liver and pancreas transplantation, the treatment of benign conditions such as acute and chronic pancreatitis, and those relating to hepatobiliary infection and inflammation are also welcomed. There will be a focus on developing a multidisciplinary approach to diagnosis and treatment with endoscopic and laparoscopic approaches, radiological interventions and surgical techniques being strongly represented. *HPB* welcomes submission of manuscripts in all these areas and in scientific focused research that has clear clinical relevance to *HPB* surgical practice.

HPB aims to help its readers - surgeons, physicians, radiologists and basic scientists - to develop their knowledge and practice. *HPB* will be of interest to specialists involved in the management of hepatobiliary and pancreatic disease however will also inform those working in related fields.

Abstracted and Indexed in: MEDLINE®EMBASEPubMedScience Citation Index ExpandedAcademic Search (EBSCO)

HPB is owned by the International Hepato-Pancreato-Biliary Association (IHPBA) and is also the official Journal of the American Hepato-Pancreato-Biliary Association (AHPBA), the Asian-Pacific Hepato Pancreatic Biliary Association (A-PHPBA) and the European-African Hepato-Pancreatic Biliary Association (E-AHPBA).

IMPACT FACTOR

2016: 3.290 © Clarivate Analytics Journal Citation Reports 2017

ABSTRACTING AND INDEXING

Academic Search (EBSCO)
EMBASE
MEDLINE®
PubMed
Science Citation Index Expanded
Web of Science

EDITORIAL BOARD

T. Kent, Boston, USA
M. Krawczyk, Warsaw, Poland
P. Lai, Hong Kong, China
J.D Lendoire, Buenos Aires, Argentina
D. Mahvi, Chicago, USA
S. Maithel, Atlanta, USA
M. Makuuchi, Tokyo, Japan
R.C.G. Martin, Kentucky, USA
J. McCall, Otago, New Zealand
M. Miyazaki, Chiba, Japan
M. Ohtsuka, Chiba, Japan
S. Orloff, Portland, USA
I. Özden, Istanbul, Turkey
R. Padbury, Adelaide, Australia
R. Parks, Edinburgh, UK
T. Pawlik, Columbus, USA
H. Pitt, Philadelphia, USA
J. Powell, Edinburgh, UK
M. Rees, Basingstoke, UK
F. Rocha, Seattle, USA
A. Sauvanet, Clichy, France
R. Schulick, Denver, USA
M. Selzner, Toronto, Canada
S. Shrikhande, Mumbai, India
M. Smith, Johannesburg, USA
J. Tseng, Boston, USA
H. Uchiyama, Fukuoka, Japan
T. van Gulik, Amsterdam, Netherlands
B. Visser, Stanford, USA
C.M. Vollmer, Philadelphia, USA
J. Windsor, Auckland, New Zealand
C. Wolfgang, Baltimore, USA
T. Yang, Shanghai, China

GUIDE FOR AUTHORS

HPB Instructions for Authors

HPB publishes original articles, reviews, meta-analyses, systematic reviews and randomized clinical trials, all of which are submitted to rigorous peer review. HPB subscribes to the policies published by the International Committee of Medical Journal Editors (ICMJE) and adheres to publishing ethics guidelines published by the Committee on Publication Ethics (COPE). HPB now requires Corresponding Authors to complete an Author Statement on behalf of all co-authors before acceptance of the manuscript. The Author Statement form can be found here; copies may also be requested from the Editorial Office (HPBJournal@elsevier.com).

Manuscript submission

HPB operates an online submission and peer review syste that enables authors to submit articles online and track their progress via a web interface. Any queries regarding ScholarOne Manuscripts ro manuscript submission should be directed to the HPB Editorial Office (HPBJournal@elsevier.com).

Manuscripts should be submitted online at http://mc.manuscriptcentral.com/hpb

Article Types

Please note that HPB no longer publishes Case Studies, Technical Reports, Image of the Issue and How I do it. Authors interested in submitting manuscripts in these categories are encourage to submit to the "My HPB" website instead.

Leading articles

The Editors commission leading articles of 800-1000 words and up to ten references. A single author is preferred. Submissions may be subject to peer review and the Editors retain the right to alter textual style.

Reviews (including systematic reviews and meta-analyses

Priority will be given to work that addresses a topic of current interest. All meta-analyses of randomized trials must adhere to the guidelines outlined in the PRISMA statement, which is designed to improve manuscript quality. Authors must include a suitable PRISMA flow chart in their submission (click here for an example) as well as the checklist (upload the checklist under the file designation 'Other'). Further advice on suitability is available from the Editorial Office: HPBJournal@elsevier.com.

Reviews must include a structured abstract (maximum 200 words), should not exceed 3,500 words of text and 50 to 75 references. Figures and tables are usually limited to 4 (combined total) but in exceptional cases more may be permitted at the discretion of the editors.

Useful resources for Authors of review articles include the article 'Systematic reviews and meta-analysis for the surgeon scientist' by Galandiuk and colleagues, and the Cochrane Handbook for Systematic Reviews of Interventions.

HPB will consider for publication Cochrane review articles that have been substantially shortened and re-written for a surgical audience, but such submissions must state this on the title page of the manuscript, and copies of the original article must be sent to the editorial office for consideration. You must also apply for permission from the Cochrane Library – further information on how to do this is available in the Cochrane Manual. These articles will be subject to the usual HPB peer review process.

Prospective clinical trials

HPB expects all authors to register prospective clinical trials in a suitable electronic and freely accessible registry (e.g. www.clinicaltrials.gov, www.controlled-trials.com), according to the ICMJE guidelines1,8. For this purpose, a clinical trial is defined as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between an intervention and a health outcome. The registration number of the clinical trial should be quoted at the end of the abstract. If you wish the Editor to consider an unregistered trial, please explain why the trial has not been registered.

In addition, all randomized clinical trials must adhere to the guidelines outlined in the CONSORT statement and investigators must include a suitable CONSORT flow chart in their submission (click here for an example) as well as the checklist (upload the checklist under the file designation 'Other'). The primary end point and power calculation must be clearly stated, and randomized clinical trials should be clearly identified as such in both the title and the abstract.

Randomized clinical trials must include a structured abstract (maximum 200 words), should not exceed 3,000 words of text and 50 references. Figures and tables are usually limited to 5 (combined total) but in exceptional cases more may be permitted at the discretion of the editors.

Original articles

Original articles should normally be in the format of Introduction, Methods, Results and Discussion. Original articles must include a structured abstract of 200 words or fewer (further information can be found below), should not exceed 5,000 words of text and 50 references. Figures and tables are usually limited to 5 (combined total) but in exceptional cases more may be permitted at the discretion of the editors.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters must be no more than 250 words in length, including no more than five references.

Invited Commentary

The Editors may seek an invited commentary which will accompany a topical original article. This should normally be fewer than 500 words with no more than five references. The Editors retain the right to alter textual style.

Guidelines

Guidelines that accompany an article may be considered for publication in the journal. If you intend to prepare guidelines from a consensus meeting and are interested in submitting them to the journal please consult with the Editorial Office (HPBJournal@elsevier.com) in the first instance.

BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Originality

On submission of the manuscript the corresponding author must warrant that the article is an original work, has not been published before, and is not being considered for publication elsewhere in its final form, in either printed or electronic media.

Publication of abstracts and presentations at scientific meetings will not jeopardise full publication. Authors should declare that any republication of the data (e.g. in secondary analysis or translation) will not constitute redundant publication, will not breach copyright, and will reference the original publication.

Redundant (multiple) publication

HPB does not consider the following to be prior publication: abstracts and posters at conferences, results presented at meetings (for example, to inform investigators or participants about findings) and results databases (data without interpretation, discussion, context or conclusions in the form of tables and text to describe data/information where this is not easily presented in tabular form). Manuscripts that have been published previously in another language should state this on the title page of the submission. Manuscripts that have been previously published in English that are submitted with the aim of serving different audiences are not generally accepted by HPB (an exception to this is the publication of substantially shortened Cochrane Review articles; see section 2.b).

Editors may request copies of related publications if they are concerned about overlap and possible redundancy.

Sub-group analyses, meta-, and secondary analyses should be clearly identified as analyses of data that have already been published, and must refer to the primary source.

Research and publication misconduct

HPB adheres to COPE guidelines[ii] and will pursue cases of suspected research and publication misconduct (including falsification, fabrication, plagiarism, inappropriate image manipulation, redundant publication and authorship misdemeanours). In such cases, HPB will follow the processes set out in the COPE flowcharts12. Authors found guilty of misconduct can expect their behaviour to be reported to the head of the relevant institution, and details of the case may be highlighted in the pages of the journal13. If you have concerns regarding the legitimacy of an article published in HPB, please write to the Editorial Office: HPBJournal@elsevier.com.

Human and animal rights

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed.

Human transplantation manuscripts

The journal requires authors of human transplantation manuscripts from the Peoples Republic of China to provide statements to confirm (1) that consent was obtained to the use of donor organs for transplantation, either from the donor in life or from the family of the donor; and (2) that none of the donors were prisoners who were executed. These two statements are distinct and must both be provided before a manuscript can enter the review process. These criteria are designed to provide reassurance that ethical standards of organ donation have been met, in keeping with the editorial policy of HPB.

Editors reserve the right to reject papers if there is doubt whether appropriate procedures have been followed.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/ registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright- holder.

HPB subscribes to the policy of uniform requirements for manuscripts; this facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. HPB accepts the criteria for authorship proposed in the ICMJE 1, 10 and subscribes to the COPE guidelines on good publication practice 2. These guidelines are summarised below.

Authorship

For research papers, Authorship should be decided at the launch of the study. The Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3.

Contributors who do not qualify as Authors should be listed and their particular contribution described in the Acknowledgements section of the article. On submission of the article, the corresponding author will be asked to confirm how all individuals listed as Authors meet the appropriate authorship criteria, that no-one who qualifies for authorship has been omitted from the list, that written authorization has been received from all co-authors, that contributors and all funding sources (for Authors and Contributors) have been properly acknowledged and that authors and contributors have approved the acknowledgement of their contribution.

The corresponding author is responsible for ensuring that all authors have seen, approved and are fully conversant with the contents of the manuscript. All authors are responsible for the accuracy of the manuscript, including all statistical calculations and drug doses.

All authors listed within the manuscript must be added as co-authors of the manuscript on Scholar One at submission.

Group authorship

Results of multicentre studies may be reported under the name of the organizing group; however, the group should identify individuals who accept direct responsibility for the manuscript. These individuals should meet the criteria for authorship described above. The individual authors who accept direct responsibility for the manuscript should list the members of the larger authorship group in an appendix to their acknowledgements.

Contributors

Each author is required to declare his or her individual contribution to the article: all authors must have materially participated in the research and/or article preparation, so roles for all authors should be described. The statement that all authors have approved the final article should be true and included in the disclosure.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

For open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (more information). Permitted third party reuse of open access articles is determined by the author's choice of user license.

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing

Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies

Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the Open Access Publication Fee. Details of existing agreements are available online.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop.

PREPARATION

Preferred file formats

Manuscripts must be written in English and prepared in 12-point type in one of the standard fonts: Times New Roman, Helvetica or Courier. It must be double spaced.

The full title page, main text and tables must be submitted as a single document in Word (.doc or .docx) or Rich Text Format (.rtf). Please do not submit text in PDF format (.pdf). Figures prepared as true images (e.g., .tif, .jpg or .eps) can be submitted as separate files.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

The main text of the paper may have separate Introduction, Methods, Results and Discussion sections (these sections may not be applicable to all article types, e.g. reviews). A short Acknowledgements paragraph may also be included. When quoting specific materials, equipment and proprietary drugs, the name and address of the manufacturer must be given in parentheses. Generic names should normally be used. Any data mentioned in the abstract or discussion must be presented in the results section of the main text.

It is appreciated that there are a variety of writing styles, but the HPB editorship would like to ensure a degree of uniformity in the presentation of the manuscript. Ensure that the Abstract describes the content of the manuscript accurately. The Abstract may be all that is seen when a search engine is used and will draw potential readers to the contents of the main article. The Introduction should be focused and brief, putting the current study into context. Methodology and Results sections should be well structured and should avoid redundancy. If tables are used, avoid repetition of results in the text. Avoid the use of personal pronouns and ensure that patients are not referred to as cases. The Discussion should focus on the results of the study and discuss these in the context of the existing literature. Highlight those areas of the study that bring new information to the reader.

Tables and illustrations

Please refer to the Article Types regarding the limit of number of figures and tables for each manuscript category.

Submit each illustration as a separate file except compound figures e.g. 1a, 1b, 1c etc, which should be supplied as a single file. Tables should be included as part of the main text file at the end of the manuscript, not embedded in the text. Type each table on a new page with a brief title. Supply artwork at the intended size for printing. Line drawings are acceptable as clear black on white graphics and must be high quality. Use hatchings, not tints. All illustrations must be supplied at the correct resolution:

1200 dpi (dots per inch) for black and white line art (simple bar graphs, etc.) 300

dpi for halftones (black and white photographs).

600 dpi for combination halftones (photographs that also contain line art such as labelling or thin lines).

Illustrations in colour are encouraged and will be printed at no cost to the author. Label each illustration with the figure number and lead authors name. Indicate the top of the illustration and a measure of magnification for photomicrographs. Include explanations of symbols and shading within the figure, use arrows to identify particular areas of interest. Survival curves must be accompanied by a table giving the actual numbers of patients involved and should be truncated when the numbers at risk are small; that is, when they are less than one-third of the starting figure. Include in the legends to illustrations, and the footnotes to tables, brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Illustration services
Elsevier's WebShop offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Essential title page information

- ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
- ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Additional title page information

Please indicate; (a) the category in which the manuscript is being submitted (orignal article, review, randomized clinical trial); and (b) whether the paper is based on a previous communication to a society or meeting (with full details).

Abstract

The Abstract must contain fewer than 200 words and presented in a structured format. *Background:* state why the study was done, the main aim and the nature of the study (randomized clinical trial, retrospective review, experimental study etc). *Methods:* describe patients, laboratory material and other methods used. *Results:* state the main findings, including important numerical values. *Discussion:* state the main conclusions, highlighting controversial or unexpected observations.

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.

Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Abbreviations

Avoid using abbreviations. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Numbers and units

Provide absolute numbers always; percentages may be given in addition but never on their own (percentages are not acceptable for sample sizes less than 50). Use the decimal point, not a comma; for example 5.7. Use a space and not a comma after thousands and multiples thereof; for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics and design

Set out clearly the objectives of the study; identify the primary and secondary hypotheses, the chosen end-points and justify the sample size with a power calculation.

Clearly describe methods used for analysis; methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the P value. Actual P values should always be reported to three decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values. For detailed guidance on the handling of statistical material consult the article by Murray 11.

Expressions of data

All results should be presented as actual numbers.

For nominal data with denominators greater than 50, percentages should be given to 1 decimal place.

For continuous data non parametric descriptors (median and range) and statistical analysis (e.g. Mann Whitney U) should be performed unless it can be shown (statistically) that data are normally distributed in which case it is reasonable to use parametric tests (e.g. student t-test).

Extensive use of tables is encouraged and data provided in tables should not be repeated in text. All tables, figures and graphs must have a stand alone legend which enables interpretation without the need to refer to the text.

P values should be standardised to 3 decimal places and should include actual values for those values that are non-significant.

For Kaplan-Meier curves the following should be adhered to:

a) Numbers at risk should be given below the x-axis in line with the time value.b) Survival curves must be accompanied by a table giving the actual numbers of patients involved and each individual graph should be truncated when the numbers at risk are small; that is, the number at risk reaches the greater of either 1/10th of the original denominator or 5.c) Censored variables should be shown.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

A DOI can be used to cite and link to electronic articles where an article is in-press and full citation details are not yet known, but the article is available online. A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Reference style
Text: Indicate references by superscript numbers in the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *J Sci Commun* 2010;**163**:51–9.
Reference to a book:
2. Strunk Jr W, White EB. *The elements of style.* 4th ed. New York: Longman; 2000.
Reference to a chapter in an edited book:
3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. *Introduction to the electronic age,* New York: E-Publishing Inc; 2009, p. 281–304.
Reference to a website:
4. Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003].
Reference to a dataset:
[dataset] 5. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.
Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;**277**:927–34)(see also Samples of Formatted References).

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

Video
Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. . In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary material
Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

AFTER ACCEPTANCE

Proofs
One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or, a link will be provided in the e-mail so that authors can download the files themselves. Elsevier now provides authors with PDF proofs which can be annotated; for this you will need to download the free Adobe Reader, version 9 (or higher). Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site.

If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and scan the pages and return via e-mail. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Webshop. Corresponding authors who have published their article open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also check the status of your submitted article or find out when your accepted article will be published.

Ethical Approval

Unidade de Investigação

Tomei conhecimento. Nada a opor.

23 de Janeiro de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

Aprovado. Ao CA DIRECÇÃO CLÍNICA 17/1/18

(Prof.ª Doutora Ana Azevedo)

n.º 270 / 17

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 08 FEV 2018

Presidente do Conselho de Administração

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

Nome do Investigador Principal:

Raquel Jorge Domingues Palhau

Título da Investigação:

Fatores associados a maior sobrevida após ressecção de metástases hepáticas de Carcinoma do Cólon e Reto – estudo retrospetivo

Pretendendo realizar no(s) Serviço(s) de:

Cirurgia Geral do Centro Hospitalar São João (CHSJ)

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 25 *de* Outubro *de* 2017 .

Raquel Jorge Domingues Palhau

assinatura

CES-IM005-0

Parecer da Comissão de Ética para a Saúde do

Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Fatores associados a maior sobrevida após ressecção de metástases hepáticas de Carcinoma do Cólon e Reto – estudo retrospetivo

Nome da Investigadora Principal: Raquel Jorge Domingues Palhau, aluna do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: No Serviço de Cirurgia Geral do CHSJ. Dispõe de autorização do Dr. José da Costa Maia.

Objectivos do Estudo:

- Avaliar a sobrevida dos doentes submetidos a resseção de metástases hepáticas de CCR
- Determinar os fatores associados a melhor sobrevida
- Comparar a sobrevida no CHSJ com os resultados dos melhores centros

Insere-se no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação do Dr. Marinho José Soares Ferreira Almeida, que será também o profissional de ligação.

Concepção e Pertinência do estudo:

O Carcinoma do Cólon e Reto (CCR) mantém-se como a terceira causa de morte por cancro, apesar dos esforços promovidos na deteção precoce e existência de tratamentos mais eficazes. Cerca de 33% dos doentes atingidos desenvolverá metastização hepática, síncronas ou metácronas. Na ausência de doença extra-hepática, a cirurgia das lesões secundárias pode ser curativa, com sobrevida aos 5 anos entre os 36-58%. No entanto, a grande maioria dos doentes apresenta metástases hepáticas irressecáveis ad initium, quer pelo seu tamanho, localização ou remanescente hepático funcional. Os avanços na quimioterapia, nas técnicas de modulação hepática e na abordagem percutânea permitem, em muitos casos, reduzir e tornar ressecável estas lesões. Atualmente, no Centro Hospitalar de São João (CHSJ) a existência de equipas multidisciplinares permite otimizar os recursos e adequar o esquema terapêutico a cada doente, equacionando o timing e a relação com a cirurgia de terapêuticas tão diversas como: a quimioembolização transarterial (TACE), a radiofrequência, a radioterapia locoregional, assim como, a quimioterapia sistémica.

Existem na literatura vários estudos que apresentam os fatores prognósticos que auxiliam na previsão da sobrevida a curto e a longo prazo, destes doentes, após a resseção hepática, e diversos autores desenvolveram scores pré-operatórios com base nos mesmos, ainda que não exista consenso. Este tema tem sido pouco estudado no nosso país e um estudo dentro deste âmbito poderá auxiliar na seleção dos doentes candidatos a ressecção de doença hepática metastáticas do Carcinoma do Colon e do Reto.

De forma a responder aos objetivos delineados será desenvolvido um estudo de cariz retrospetivo. A amostra a ser estudada será constituída por doentes submetidos a cirurgia de metástases hepáticas de CCR com 5 anos de sobrevida. Estão claros os critérios de inclusão no estudo, bem como as variáveis a serem estudadas.

Não é referido o período do estudo nem é claro como serão obtidos os dados retrospetivos dos doentes incluídos. Questiona-se também de que forma irá aceder aos dados que lhe permitem avaliar a sobrevida dos doentes incluídos no estudo.

Benefício/risco: NA

Confidencialidade dos dados:
De acordo com as normas em vigor, os doentes serão designados por código, não sendo divulgado o nome/identidade, protegendo, desta forma, o anonimato no decorrer de toda a investigação.

Respeito pela liberdade e autonomia do sujeito de ensaio: NA

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: março de 2018

Conclusão: Proponho um parecer favorável à realização deste projeto de investigação, **desde que clarificados os aspetos assinalados a itálico.**

Porto, 15 de dezembro de 2017

O Relator da CES,

Comissão de Ética

De: Raquel Palhau [raquel_palhau@hotmail.com]
Enviado: sexta-feira, 5 de Janeiro de 2018 15:38
Para: Comissão de Ética
Assunto: Re: Pedido de esclarecimentos CES

Boa tarde,

Desde já Bom ano e peço desculpa por só responder agora mas tenho tido alguns problemas em aceder ao meu mail.

No estudo só serão incluídos os doentes que foram submetidos a recessão hepática até Dezembro de 2012 (prevê-se incluir doentes submetidos a recessão hepática entre Outubro 2006-Outubro 2012), de forma a perfazer 5anos de sobrevida pós-op da recessão hepática. Existe uma base de dados com o número dos processos dos doentes submetidos a recessão hepática na unidade hepatobiliar do serviço de Cirurgia Geral do CHSJ. Será a partir desta base de dados que se avaliará cada doente individualmente através do SClinic (nomeadamente registo das consultas, intervenções cirúrgicas, resultados anatomo-patológicos, exames auxiliares de diagnóstico, registo de óbito entre outros) sendo exclusivamente usada esta plataforma para a recolha dos dados retrospectivos e avaliada a sobrevida.
Espero ter conseguido esclarecer as questões colocadas.
Obrigada pela atenção.

Os melhores cumprimentos
Raquel Palhau

De: Comissão de Ética <comissao.etica@hsjoao.min-saude.pt>
Enviado: 15 de dezembro de 2017 15:20
Para: raquel_palhau@hotmail.com
Assunto: Pedido de esclarecimentos CES

SÃO JOÃO

Orgãos e Comissões de Apoio Técnico
Comissão de Ética para a Saúde

Exma. Sra. Dra. Raquel Jorge Domingues Palhau

Em anexo envio parecer relativo ao protocolo 270-17 'Fatores associados a maior sobrevida após ressecção de metástases hepáticas de carcinoma do cólon e reto - estudo retrospetivo'.
Aguardamos o esclarecimento das questões assinaladas para a emissão de um parecer conclusivo.

Com os melhores cumprimentos,

Pedro Brito
(Comissão de Ética para a Saúde)

São claras a adequação das respostas às questões levantadas. Pode a opor.
12-1-18

ADENDA AO PROTOCOLO DE ESTUDO

Exmo. Senhor Presidente do Conselho de Administração do Centro Hospitalar de São João,

Venho por este meio pedir autorização para a alteração do título e objetivo do estudo, que obteve aprovação da CES e autorização do CA, no dia 7 de fevereiro de 2018, com o número 270/17.

Desta forma, pede-se a alteração do título de "Fatores associados a maior sobrevida após ressecção de metástases hepáticas de carcinoma do cólon e reto - estudo retrospetivo" para "Fatores associados a recorrência em doentes com 5 anos de sobrevida após resseção de metástases hepáticas de cancro colo-rectal/Factors associated with recurrence in patients with 5-year survival after resection of colorectal cancer liver metastases".

Pede-se, igualmente, a alteração dos objetivos do projeto (avaliar a sobrevida dos doentes submetidos a resseção de metástases hepáticas de carcinoma colorectal (CRC), determinar os fatores associados a melhor sobrevida e comparar a sobrevida no CHSJ com os resultados dos melhores centros) para:

- Avaliar a recidiva/recorrência e o tempo livre de doença em doentes submetidos a ressecção de metástases hepáticas de (CRC)
- Determinar os fatores associados a recorrência e tempo livre de doença
- Comparar a recorrência dos doentes no CHSJ com os resultados de outros centros

O grupo de estudo, variáveis e o método de recolha de informação seriam os mesmos, pretender-se-ia apenas clarificar que os doentes seriam comparados relativamente à existência de recorrência, sendo que, os doentes seriam divididos e comparados entre 3 grupos: sem recorrência, recorrência em menos 12 meses e recorrência após 12 meses.

Aguardo apreciação e parecer.

Os melhores cumprimentos

Raquel Jorge Domingues Ribeiro

A Autora propõe nas futuras questões éticas que se proponha uma Lista Formal e sua implementação.

2018.03.21

Prof. Doutor Fil[illegible]
Presidente da Comissão de Ética

LISTA DE DOCUMENTOS ANEXOS

- ☐ Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- ☐ Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- ☒ Protocolo do estudo
- ☒ Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- ☒ Profissional de ligação
- ☐ Informação dos orientadores
- ☐ Informação ao participante
- ☐ Modelo de consentimento
- ☐ Instrumentos a utilizar *(inquéritos, questionários, escalas, p.ex.)*: _____
- ☒ Curriculum Vitae abreviado *(máx. 3 páginas)*
- ☐ Protocolo financeiro
- ☐ Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 25 *de* Outubro *de* 2017

Nome legível: Raquel Jorge Domingues Palhau

Raquel Jorge Domingues Palhau
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de ____ / ____ / ____

15/12/17

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

Centro Hospitalar **São João**

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

12/01/18